

# Utility of B-Natriuretic Peptide in Detecting Diastolic Dysfunction

## Comparison With Doppler Velocity Recordings

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**Background**—Although Doppler echocardiography has been used to identify abnormal left ventricular (LV) diastolic filling dynamics, inherent limitations suggest the need for additional measures of diastolic dysfunction. Because data suggest that B-natriuretic peptide (BNP) partially reflects ventricular pressure, we hypothesized that BNP levels could predict diastolic abnormalities in patients with normal systolic function.

**Methods and Results**—We studied 294 patients referred for echocardiography to evaluate ventricular function. Patients with abnormal systolic function were excluded. Cardiologists making the assessment of LV function were blinded to BNP levels. Patients were classified as normal, impaired relaxation, pseudonormal, and restrictivelike filling patterns. Patients diagnosed with evidence of abnormal LV diastolic function (n=119) had a mean BNP concentration of  $286 \pm 31$  pg/mL; those in the normal LV group (n=175) had a mean BNP concentration of  $33 \pm 3$  pg/mL. Patients with restrictivelike filling patterns on echocardiography had the highest BNP levels ( $408 \pm 66$  pg/mL), and patients with symptoms had higher BNP levels in all diastolic filling patterns. The area under the receiver-operating characteristic curve for BNP to detect any diastolic dysfunction was 0.92 (95% CI, 0.87 to 0.95;  $P < 0.001$ ). A BNP value of 62 pg/mL had a sensitivity of 85%, a specificity of 83%, and an accuracy of 84% for detecting diastolic dysfunction.

**Conclusions**—A rapid assay for BNP can reliably detect the presence of diastolic abnormalities on echocardiography. In patients with normal systolic function, elevated BNP levels and diastolic filling abnormalities might help to reinforce the diagnosis diastolic dysfunction. (*Circulation*. 2002;105:595-601.)

**Key Words:** echocardiography ■ peptides ■ diastole

Abnormalities of diastolic function may play a major role in patients with signs and symptoms of congestive heart failure (CHF).<sup>1,2</sup> However, diastolic function is determined by a complex sequence of interrelated events that may render abnormalities difficult to diagnose and the success of treatment difficult to assess.<sup>3</sup> Although Doppler echocardiography has been used to examine left ventricular (LV) diastolic filling dynamics, the limitations of this technique suggest the need for other objective measures of diastolic dysfunction.<sup>4</sup> In patients with normal systolic function, there is currently no blood test that can rapidly identify patients with diastolic dysfunction.<sup>5</sup>

B-natriuretic peptide (BNP) is a cardiac neurohormone secreted from the ventricles in response to ventricular volume expansion and pressure overload.<sup>6,7</sup> BNP levels are known to be elevated in patients with symptomatic LV dysfunction and correlate to NYHA class and prognosis.<sup>8-13</sup> BNP levels may also reflect diastolic dysfunction.<sup>14,15</sup> In the present study, a rapid assay for BNP was used to detect abnormal diastolic flow properties in patients referred for echocardiography regardless of the presence of previously documented CHF.

## Methods

### Study Population

The study was approved by the University of California Institutional Review Board. A sample of 294 patients referred for echocardiography to evaluate LV function at the San Diego Veteran's Healthcare System and Thornton Hospital between June 1999 and November 2000 was studied. Patients whose referral was to assess valve disease, to determine whether a vegetation was present, or to rule out a cardiac cause of stroke were excluded ( $\approx 10\%$ ). Patients with an ejection fraction  $< 50\%$  or an LV end-diastolic dimension  $> 5.5$  mm were excluded. Patient referrals were made by either clinic physicians or nurse practitioners. About 5% of patients offered consent refused.

### Echocardiography

M-mode and 2D images and spectral and color flow Doppler recordings were obtained with commercially available instruments operating at 2.0 to 3.5 MHz. Two-dimensional imaging examinations were performed in the standard fashion in parasternal long- and short-axis views and apical 4- and 2-chamber views.<sup>16</sup> Pulsed Doppler spectral recordings were obtained in the apical 4-chamber view from a  $4 \times 4$ -mm sample volume positioned at the tips of the mitral leaflets and in the right upper paraseptal pulmonary vein and adjusted to yield velocity signals of maximal amplitude. All data

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were hard copied to 1/2-in VHS videotape for subsequent playback, analysis, and measurement.

Two-dimensional echocardiograms were subjected to careful visual analysis to detect regional contractile abnormalities. LV systolic and diastolic volumes and ejection fraction were derived from biplane apical (2- and 4-chamber) views with a modified Simpson's rule algorithm.<sup>17</sup> Left atrial and LV dimensions were measured from M-mode images according to standard criteria.<sup>16</sup> The transmitral pulsed Doppler velocity recordings from 3 consecutive cardiac cycles were used to derive measurements as follows: E and A velocities were the peak values reached in early diastole and after atrial contraction, respectively, and deceleration time (DT) was the interval from the E-wave peak to the decline of the velocity to baseline. In those cases in which velocity did not return to baseline, extrapolation of the deceleration signal was performed. In addition, pulmonary venous systolic and diastolic flow velocities were obtained as the maximal values reached during the respective phase of the cardiac cycle, and the pulmonary venous "A" reversal was the maximal velocity of retrograde flow into the vein after the P wave of the ECG. Finally, the LV isovolumetric relaxation time (IVRT) was obtained in the apical 5-chamber view with a continuous-wave cursor or, if possible, a pulsed Doppler sample volume positioned to straddle the LV outflow tract and mitral orifice to obtain signals from aortic valve closure, the termination of ejection and mitral valve opening, or the onset of transmitral flow. IVRT was taken as the time in milliseconds from the end of ejection to the onset of LV filling. All echocardiograms were interpreted by experienced cardiologists who were blinded to the BNP levels.

## Echo Classifications

### *Normal Ventricular Function*

Normal ventricular function was defined by normal LV end-diastolic (3.5 to 5.5 cm) and end-systolic (2.5 to 3.6 cm) dimensions, no major wall motion abnormalities, an ejection fraction >50%, and no evidence of impaired or restrictivelike relaxation abnormalities as described below.

### *Systolic Dysfunction*

Systolic dysfunction was defined by an ejection fraction <50% or any wall motion abnormalities. Patients with systolic dysfunction were excluded.

### *Diastolic Dysfunction*

Diastolic dysfunction was classified in 3 categories.

### *Impaired Relaxation*

Impaired relaxation was defined as an E/A ratio <1 or DT >240 ms in patients <55 years of age and an E/A ratio <0.8 and DT >240 ms in patients ≥55 years of age. IVRT measurement, available in approximately one half of the patients, was >90 ms in 60% of patients with abnormal E/A changes and/or DT >240 ms.

### *Pseudonormal*

Pseudonormal was defined as an E/A ratio of 1 to 1.5 and DT >240 ms. Confirmation included PVd/PVs >1.5 or IVRT <90 ms or by reversal of the E/A ratio (to <1.0) by Valsalva when possible.

### *Restrictivelike*

Restrictivelike filling patterns were defined as DT <160 ms with ≥1 of the following: left atrial size >5 cm, E/A >1.5, IVRT <70 ms, PVd/PVs >1.5, and pulmonary "A" reversal duration exceeding forward mitral A-wave duration. Eighty-five percent of patients had ≥2 abnormalities, and 51% had ≥3 abnormalities.

### *Chamber Abnormalities*

Left atrial enlargement was defined as left atrial size ±5.0 cm. LV hypertrophy was defined as mean LV wall thickness of septum and posterior wall ±1.2 cm. Patients with hypertrophic cardiomyopathy were excluded.

## History of CHF and Clinical CHF

Patients were queried as to whether they had any history of CHF. In addition, medical records were examined for objective findings of CHF, including abnormalities on the physical examination, hospitalization for CHF, or regular visits to the cardiomyopathy clinic. Patients without a history of CHF were additionally characterized by the lack of any prior study of LV function. Clinical CHF was determined to be present by cardiologists who were blinded to the echocardiogram results on the basis of standard Framingham criteria, admission and treatment for CHF, and emergency department visits for CHF.

## Measurement of BNP Levels

All samples were collected by venipuncture into EDTA tubes. The blood samples were kept at room temperature and analyzed within 4 hours of the draw time. Before analysis, each tube was inverted several times to ensure homogeneity. The whole blood was then analyzed in triplicate with the Triage BNP assay. In some cases, the sample was centrifuged and plasma was removed, allocated, and frozen at -70°C before analysis. The BNP assay is a sandwich immunoassay that consists of a disposable device to which 250 μL of EDTA-anticoagulated whole blood or plasma is added. The Triage meter was used to measure the BNP concentration by detecting a fluorescent signal that reflects the amount of BNP in the sample.

Once 250 μL of whole blood or plasma was added to the device, the cells were separated from the plasma by a filter, and the plasma containing BNP entered a reaction chamber that contained fluorescent-tagged BNP antibodies to form a reaction mixture. The reaction mixture was incubated for ≈2 minutes and then migrated through the diagnostic lane by capillary action to a zone of immobilized antibody that would bind the desired BNP-fluorescent antibody complex. The unbound fluorescent antibodies were washed away by the excess sample fluid. After ≈15 minutes, the device was placed into the Triage meter that measured the fluorescence intensity of the BNP assay zone. The Triage meter then correlated the fluorescence measurement to the BNP concentration by use of an internal calibration curve. The assay was completed in ≈15 minutes. Precision, analytical sensitivity, interferences, and stability have all been previously described.<sup>9</sup>

## Statistical Analysis

Group comparisons of BNP values were made by use of *t* tests for independent samples and ANOVA with post hoc Tukey tests when indicated. In all cases, these were computed with raw BNP values and repeated with log-transformed BNP values because the BNP distribution was positively skewed. Both versions yielded the same conclusions. Results are expressed as mean±SEM for the raw values. Sensitivity, specificity, and accuracy were computed for BNP by use of a selection of possible cut points. The diagnostic utility of BNP alone was compared with the echocardiographic probability of LV dysfunction through the use of receiver-operating characteristic (ROC) curves. Results are expressed in terms of the area under the curve (AUC) and 95% CI for this area. Logistic regression was used in a multivariate approach for evaluating the ability of BNP to identify diastolic dysfunction over and above the information provided by other indicators. To produce ORs, cut points were used for age (65 years) and BNP (62 pg/mL) to reduce them to nominal variables.

## Results

The characteristics of all 294 patients are shown in Table 1. Most subjects were male. Patients were divided into 2 groups on the basis of whether they manifested normal or abnormal LV diastolic function by echocardiography. Among those patients with normal findings, 5% had clinical CHF, 34% had shortness of breath, and 19% had pedal edema. Two patients with normal LV diastolic function had a history of CHF. Patients with abnormal echocardiograms were older and more

**TABLE 1. Patient Demographics**

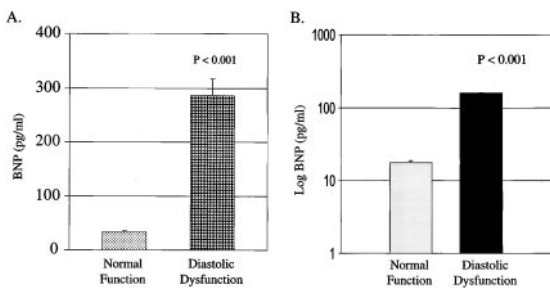
Demographics	No Diastolic Dysfunction (n=175)	Diastolic Dysfunction (n=119)
Age, y	60±1	71±1
Sex, M/F	159/16	106/13
Hypertension, %	58	79
Diabetes mellitus, %	35	54
Coronary artery disease, %	26	50
Shortness of breath, %	34	46
Edema, %	19	29
History of CHF, %	1	21

likely to have clinical CHF (35%), shortness of breath (46%), and edema (29%). Hypertension, diabetes, and coronary artery disease were more prevalent in patients with abnormal diastolic function on echocardiography.

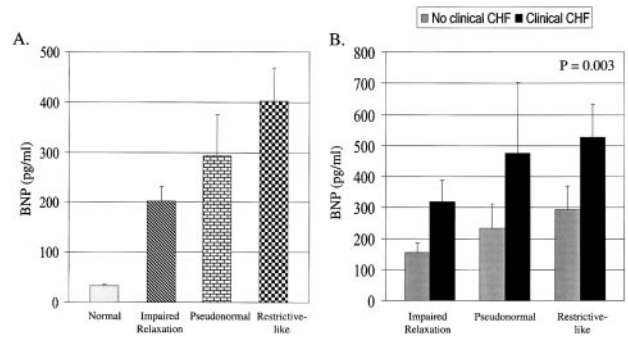
**BNP Levels and Ventricular Dysfunction**

Figure 1 represents the BNP levels in the normal and abnormal diastolic function groups. The difference between groups was significant in both raw ( $P<0.001$ ) and log ( $P<0.001$ ) form. Patients diagnosed with abnormal diastolic function (n=119) had a mean BNP concentration of  $286\pm 31$  pg/mL, whereas the normal subjects (n=175) had a mean BNP concentration of  $33\pm 3$  pg/mL. Figure 2 depicts BNP levels in the 3 mitral valve flow patterns of diastolic dysfunction. All subgroups had higher BNP levels than normal subjects ( $P<0.001$ ). Patients with the restrictivelike filling pattern had significantly higher BNP levels than patients with impaired relaxation ( $408\pm 66$  versus  $202\pm 30$  pg/mL,  $P<0.001$ ). As a group, patients with diastolic dysfunction and symptoms had higher BNP levels than those patients with asymptomatic diastolic dysfunction (Figure 2B).

The ability of BNP to detect abnormal diastolic function in patients with normal systolic function was assessed with ROC analysis (Figure 3). The AUC for the ROC curve with BNP used to detect any abnormal diastolic dysfunction was 0.91 (95% CI, 0.89 to 0.95;  $P<0.001$ ). A BNP value of 62 pg/mL had a sensitivity of 85%, a specificity of 83%, and an accuracy of 84% for detecting abnormal diastolic dysfunction when systolic function was normal. The ability of BNP to independently detect various patterns of diastolic filling in



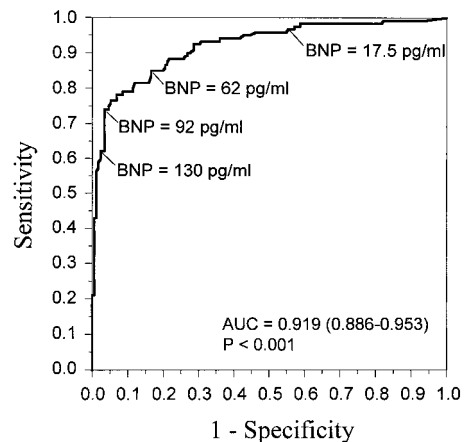
**Figure 1.** BNP levels in patients with normal function by echocardiography and with diastolic function (all filling patterns). Data are expressed as both mean±SEM (A) and geometric log mean (B). Both were significant by  $P<0.001$ .



**Figure 2.** A, Mean±SEM for normal BNP values vs impaired relaxation, pseudonormal, and restrictivelike filling patterns. Each abnormal group was different from normal group by post hoc Tukey tests ( $P<0.001$ ). B, Comparison of 3 diastolic filling patterns subdivided by whether patients had symptoms. Values are mean±SEM. Subgroups of diastolic dysfunction patients with clinical CHF overall had higher BNP levels than those without symptoms.  $P<0.05$  by post hoc Tukey test.

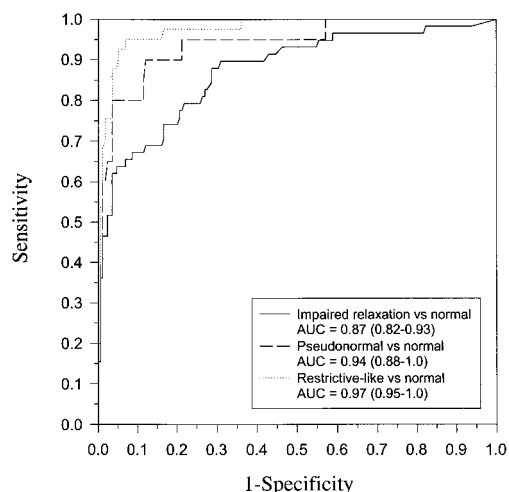
patients with normal systolic function was assessed with ROC analysis (Figure 4). Each ROC curve assesses the specific filling pattern compared with only those patients with normal systolic function (other filling patterns excluded). Although BNP levels could significantly detect all patterns of filling in patients with normal ejection fractions, BNP was most accurate in predicting the restrictivelike filling pattern, with an AUC of 0.98 (95% CI, 0.95 to 0.97;  $P<0.001$ ). BNP levels were not able to differentiate the various diastolic filling patterns (data not shown).

Logistic regression was used in a multivariate approach to evaluate the ability of BNP to identify diastolic dysfunction



BNP (pg/mL)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
17.5	97 (92-99)	45 (37-52)	54 (47-61)	95 (88-98)	66
62	85 (77-90)	83 (77-88)	78 (70-84)	85 (83-93)	84
92	74 (65-81)	98 (94-99)	96 (89-98)	85 (79-89)	88
130	62 (53-71)	98 (94-99)	95 (87-98)	79 (73-84)	83

**Figure 3.** ROC curve comparing sensitivity and specificity of BNP and echocardiographic diagnosis of LV diastolic dysfunction. Patients with abnormal systolic function were excluded. Select BNP values are indicated (pg./mL). Below are accuracies of various cut points of BNP. AUC is significant ( $P<0.001$ ).



**Figure 4.** ROC curve comparing sensitivity and specificity of BNP and echocardiographic diagnosis of various diastolic filling patterns. Patients with abnormal systolic function were excluded. AUC is significant ( $P < 0.001$ ) for each diastolic filling abnormality vs patients with normal systolic function (patients with other diastolic filling abnormalities excluded in each analysis).

over and above the information provided by other indicators. All variables identified in Table 1 and BNP were used as independent variables in this analysis, and the presence of diastolic dysfunction was the dependent variable. To produce ORs, cut points were used for age (65 years) and BNP (62 pg/mL) to reduce them to nominal variables. The results are summarized in Table 2. Age, history of CHF, and BNP each contributed significantly to the identification of diastolic dysfunction. The OR for BNP was 26.8 (95% CI, 12.51 to 57.42).

### Correlation of Left Atrial Enlargement and LV Hypertrophy to BNP Elevation

The frequency of patients with left atrial enlargement, LV hypertrophy, or the 3 different diastolic filling abnormalities

**TABLE 2. Logistic Regression in a Multivariate Approach for Evaluating the Ability of BNP to Identify Diastolic Dysfunction Over and Above the Information Provided by Other Indicators**

Indicator	<i>P</i>	OR	95% CI
Age >65 y	<0.001	3.91	1.84–8.29
Male sex	0.886	0.92	0.28–3.03
Hypertension	0.169	1.78	0.78–4.03
Diabetes mellitus	0.632	1.21	0.56–2.62
Coronary artery disease	0.344	1.45	0.67–3.1
Shortness of breath	0.934	1.03	0.48–2.23
Edema	0.257	0.59	0.24–1.46
History of CHF	<0.001	26.6	4.71–150.33
BNP >62 pg/mL	<0.001	26.8	12.51–57.42

All variables in Table 1 and BNP were used as independent variables in this analysis, and the presence of diastolic dysfunction was the dependent variable. To produce ORs, cut points were used for age (65 years) and BNP (62 pg/mL) to reduce them to nominal variables. The OR for BNP was 26.8 (95% CI, 12.51 to 57.42).

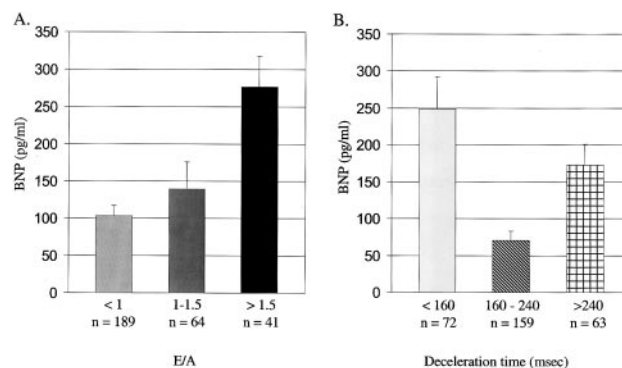
**TABLE 3. Chamber Enlargement and Diastolic Filling Abnormalities**

	Average BNP, pg/mL	BNP <62 pg/mL, %	BNP ≥62 pg/mL, %
Left atrial enlargement, (n=136)	209±26	34.60	65.40
LV hypertrophy (n=120)	170±23	41.70	58.30
Left atrial enlargement and LV hypertrophy (n=63)	231±34	17.50	82.50
Impaired relaxation (n=58)	202±30	25.90	74.10
Pseudonormal (n=20)	294±83	10	90
Restrictive (n=41)	402±66	2.40	97.60

Chamber enlargement and diastolic filling abnormality in relation to BNP cut point of 62 pg/mL, which gave both sensitivity and specificity in the 80% range. Data are presented as mean±SEM and percent of patients with the specific abnormality above or below the cut point.

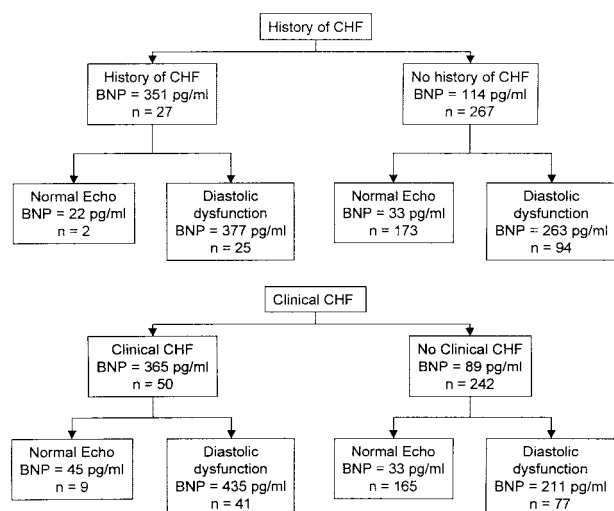
in whom BNP levels were above the ROC-generated cut point of 62 pg/mL is presented in Table 3. Within each abnormal filling pattern group, most patients had BNP levels greater than, rather than less than, the cut point of 62 pg/mL. Only 2% of patients with the restrictivelike filling pattern had BNP levels <62 pg/mL. Of note is that the percentage of patients with the combination of left atrial enlargement and LV hypertrophy who had BNP levels greater than the cutoff of 62 pg/mL was just as high as the percentage of patients with impaired relaxation, even though this combination was present in approximately half the cases of impaired relaxation (82% versus 74%,  $P = NS$ ).

Figure 5 shows the BNP levels as a reflection of E/A ratios and DTs. BNP levels were highest in patients with E/A ratios >1.5 (227±61 pg/mL) and in those patients with DTs <160 ms (249±43 pg/mL). In patients with E/A ratios >2.0 (n=16), the BNP level was 339±87 pg/mL (not shown). In patients with E/A ratios in the normal range (1 to 1.5), BNP levels were 139±65 pg/mL. However, when this group was separated by DTs, those with normal DTs (160 to 240 ms) had mean BNP levels of only 77±34 pg/mL.



**Figure 5.** BNP levels expressed as reflection of E/A ratios and DTs. Values are mean±SEM. BNP levels were highest in patients with E/A ratios >1.5 (227±61 pg/mL) and in those patients with DTs <160 ms (249±43 pg/mL). In patients with normal E/A ratio (1 to 1.5), BNP levels were 139±65 pg/mL. However, when this group was separated by DTs, those with normal DTs (160 to 240 ms) had mean BNP levels of only 77±34 pg/mL.





**Figure 6.** BNP levels and echocardiographic findings in all patients based on presence or absence of history of CHF. Patients without history of CHF had no previous studies of LV function. This group includes both outpatients and inpatients.

### History of CHF and Symptomatic CHF

Figure 6 (top) is a breakdown of all patients based on the presence or absence of history of CHF. Among the patients with no documented history of CHF and no past determination of LV function, 35% had abnormal diastolic filling patterns. In this group, BNP levels were significantly higher ( $263 \pm 31$  pg/mL) than in the 65% of patients with no history of CHF and a normal echocardiogram ( $33 \pm 3$  pg/mL,  $P < 0.001$ ). In patients with normal systolic function and clinical CHF (Table 3, bottom), those with diastolic dysfunction on echocardiography ( $n = 41$ ) had BNP levels of  $435 \pm 41$  pg/mL, much higher than those with clinical CHF and a normal echo ( $n = 9$ , BNP = 45 pg/mL;  $P < 0.001$ ). In patients with normal systolic function and no clinical CHF, those with diastolic dysfunction on echocardiography ( $n = 211$ ) had BNP levels of  $211 \pm 77$  pg/mL, higher than those with no clinical CHF and a normal echocardiogram ( $n = 135$ , BNP = 33 pg/mL,  $P < 0.001$ ).

### Discussion

As many as 40% to 50% of patients with a diagnosis of heart failure have normal systolic function, which implicates diastolic dysfunction as the most likely potential abnormality responsible for this disorder.<sup>1,2</sup> The prevalence of diastolic heart failure increases with age, with an approximate incidence of 15% to 25% in patients <60 years of age, 35% to 40% in those between 60 and 70 years of age, and 50% in patients >70 years of age.<sup>18,19</sup> With few exceptions, diastolic heart failure cannot be distinguished from systolic heart failure on the basis of history, physical examination, chest x-ray, and ECG alone.<sup>1-3</sup> Rather, the diagnosis of abnormal diastolic performance is based on exclusion—ie, the absence of systolic dysfunction in patients with clinical CHF. The results of this study indicate that BNP represents a blood marker providing positive evidence of the presence of diastolic dysfunction.

Optimal characterization of diastolic function requires simultaneous measurement of LV pressure and volume to generate pressure-volume curves. This approach is not only invasive and imperfect but also more time consuming than is feasible in most clinically active laboratories. As a result, indirect noninvasive assessments of LV filling dynamics have been used to characterize diastolic properties.<sup>20,21</sup> Appleton et al<sup>22</sup> laid the foundation for applying Doppler transmitral velocity measurements to the evaluation of diastolic function and described 4 distinct patterns (normal, delayed relaxation, pseudonormal, and restrictive),<sup>23</sup> which have become the Rosetta stone for the clinician in diagnosing diastolic dysfunction.<sup>24</sup> However, pitfalls in the echo-Doppler assessment of diastolic dysfunction exist, and the transmitral velocity pattern can be altered by changes in heart rate, preload, afterload, contractility, valvular regurgitation, and position of the sample volume.<sup>4</sup> A simple, rapid blood test that reflects diastolic dysfunction in settings in which systolic function is normal would be of significant clinical benefit. The test should reliably rule out LV diastolic dysfunction with an adequate positive predictive value.

BNP is a 32-aa polypeptide containing a 17-aa ring structure common to all natriuretic peptides.<sup>6</sup> Unlike ANP, whose major storage sites include the atria and ventricles, the major source of plasma BNP is cardiac ventricles.<sup>25,26</sup> This suggests that BNP may be a more sensitive and specific indicator of ventricular disorders than other natriuretic peptides.<sup>6,26,27</sup> Unlike ANP, BNP has minimal presence in storage granules.<sup>25,26</sup> BNP release appears to be directly proportional to ventricular volume expansion and pressure overload.<sup>7,25,26</sup> BNP is an independent predictor of high LV end-diastolic pressure<sup>12</sup> and is more useful than ANP or norepinephrine for assessing mortality in patients with chronic CHF.<sup>26</sup>

We have previously demonstrated that a rapid assay for BNP can accurately rule out the presence of abnormal echocardiographic findings, be they systolic or diastolic.<sup>28</sup> This study extends those findings to patients with normal systolic function. In this group of patients, elevated BNP levels accurately depicted diastolic abnormalities seen on echocardiography, regardless of whether the patient had a history or symptoms of heart failure. Although BNP levels alone cannot differentiate between systolic and diastolic dysfunction, a low BNP level in the setting of normal systolic function by echocardiography may be able to rule out clinically significant diastolic abnormalities seen on echocardiography. On the other hand, elevated BNP levels in patients with normal systolic function, especially older patients with a history of CHF, correlate to diastolic abnormalities on Doppler studies. Our ROC curve of 0.92 is similar to that of the prostate-specific antigen for prostate cancer detection, which had an AUC of 0.94, and is superior to those of Pap smears and mammography (AUC = 0.70 and 0.85, respectively).<sup>29-31</sup>

### Correlation of Left Atrial Enlargement and LV Hypertrophy to BNP Elevation

As demonstrated in several studies of patients with severe LV systolic dysfunction, the inverse correlation of DT with mean left atrial pressure or pulmonary capillary wedge pressure is

excellent.<sup>32</sup> Short DTs nearly always indicate a mean left atrial mean pressure >25 mm Hg. Because BNP is a reliable indicator of elevated LV pressure,<sup>7</sup> one would assume that correlations of BNP to restrictivelike filling patterns would be high. The data presented here support these findings. By ROC curve analysis, BNP levels were extremely accurate at predicting diastolic restrictivelike abnormalities on echocardiograms. Only 2% of patients with a restrictivelike pattern on echocardiography had BNP levels less than the cutoff of 62 pg/mL, translating to a very high negative predictive value. Patients with DTs <160 ms had BNP levels of  $249 \pm 43$  pg/mL compared with  $70 \pm 13$  pg/mL in patients with normal DTs. In a previous study, we found that patients with abnormal systolic function plus shortened DT had the highest BNP levels.<sup>28</sup> Interestingly, this group of patients has also been shown to have the worst prognosis of all echocardiographic classifications of LV dysfunction because they virtually always have advanced systolic dysfunction.<sup>33</sup>

### Echocardiography and Diastolic Dysfunction

Although impaired LV relaxation has often been reported in patients with normal LV systolic function, a restrictive pattern of diastolic dysfunction has usually been observed only in patients with an advanced degree of systolic dysfunction. In the present study, we observed a group of CHF patients with normal LV size and contraction in whom  $\geq 1$  criteria for restrictive filling were exhibited on Doppler recordings, the most common being a DT of <160 ms. Such DTs would be most unusual in the older age group included in the present study. Furthermore, other diastolic abnormalities were observed in 85% of patients. We have chosen to call these findings restrictivelike and think that the higher BNP values represent a more advanced degree of dysfunction in these patients than in those with impaired relaxation. The pattern of partial expression of restrictive LV filling has not previously been appreciated and may provide an additional important tool for recognizing the presence of diastolic dysfunction by echocardiography.

### Are BNP measurements Ready To Be Part of a "Gold Standard" for Diagnosing Diastolic Dysfunction?

Numerous clinical trials have documented beneficial therapies for systolic heart failure; however, the optimal treatment for diastolic heart failure has not yet been defined. The first step toward evaluating any potential treatment of diastolic heart failure is to develop uniform criteria for its diagnosis.<sup>34</sup> Vasan and Levy<sup>34</sup> have proposed criteria for diastolic heart failure that include objective evidence of CHF, objective evidence of normal LV systolic function in proximity to CHF, and objective evidence of LV diastolic dysfunction. Although this third criterion is not often possible because it involves cardiac catheterization, an easy-to-perform, rapid test for BNP in the setting of normal systolic function correlates with the presence or absence of diastolic abnormalities on echocardiography. A low BNP level may preclude the need for echocardiography in some patients, especially those who, even though at high risk, have no symptoms of heart failure. Elevated BNP levels, on the other hand, may indicate the

presence of LV dysfunction whether the patient has symptoms or not, warranting further cardiac workup. It should be noted that the high sensitivity and specificity of BNP are influenced by the population studied, and in this case, an a priori higher likelihood of high BNP levels coinciding with diastolic abnormalities would be expected compared with a random screen of the population covering all age groups. Thus, future studies will determine whether BNP levels can be part of a gold standard for the diagnosis of diastolic dysfunction.

Finally, BNP levels have an extra advantage in that they may provide a surrogate end point for the evaluation of various treatments of heart failure. We and others have found that falling BNP levels with treatment is associated with falling wedge pressures, a lower readmission rate to the hospital, and a better prognosis.<sup>35,36</sup> Thus, monitoring BNP levels in future treatment protocols for diastolic dysfunction may provide valuable information regarding drug efficacy and patient outcomes.

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# Corrections

The following acknowledgment was intended to appear in the article “Utility of B-Natriuretic Peptide in Detecting Diastolic Dysfunction: Comparison With Doppler Velocity Recordings” by Lubien et al, which appeared in a previous issue of the journal (*Circulation*. 2002;105:595–601).

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